Alkali Metal Alkoxide Clusters: Convenient Catalysts for the Synthesis of Methylphosphonates

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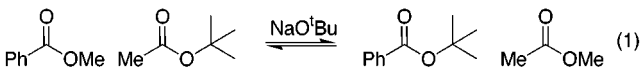
Alkali metal alkoxides are good catalysts (1−8 mol %) for promoting the interchange reaction between carbonyl and phosphorus esters. This reactivity leads to convenient methodologies for the synthesis of symmetric and unsymmetric alkyl-substituted methylphosphonates from dimethyl methylphosphonate (DMMP). Reactions rates are high with initial turnover frequencies (N_t) in excess of 1×10^6 h^{-1} observed and with KO^{t}Bu > NaO^{t}Bu > LiO^{t}Bu. The reactions were sensitive to steric effects in the product methylphosphonates with reaction rates paralleling the size of the transferring alkoxide (*n*-alkyl > isoalkyl ≫ *tert*-alkyl). For the test reaction DMMP + isopropyl acetate, substitution kinetics were consistent with a scenario wherein each methoxide is replaced sequentially, and the substitution rate for the second displacement is substantially slower than the first. Kinetic studies on the first substitution process were indicative of a concentration dependent rate law; a scenario most easily accounted for by a coupled transesterification wherein alkoxide reversibly and independently adds to phosphonate and ester.

Introduction

Phosphonate esters are important functional groups with respect to their utility as olefination reagents,[1] protecting groups in prodrugs,[2] and agrochemicals.[3] Two main synthetic methods are used for their construction. If symmetric phosphonates are desired, direct alcoholysis of alkyl dichlorophosphines followed by oxidation provides a straightforward route to these materials. Several alkyl dichlorophosphines are commercially available (e.g. Me, Et, Ph) but are expensive. Alternatively, alcoholysis of the alkyl phosphonic dichlorides can directly lead to the desired symmetric phosphonates.[4] Neither of these methods, however, is well disposed to the synthesis of phosphonates containing two different alkoxide substituents. The Michaelis-Arbuzov reaction is also a good method for the synthesis of phosphonates[5] but only works well for unhindered phosphites, and is not well suited for yielding unsymmetric phosphonates.[6] A third method, which relies on $Ti(OR)_4$/HOR-catalyzed transesterification of dialkyl phosphites, can also yield disubstituted, and in the case of *tert*-butoxy incorporation, monosubstituted products.[7] This transesterification methodology suffers, however, from long reaction times and lack of reactivity toward phosphonates.[8] A method for the synthesis of symmetric and unsymmetric phosphonates based on a common protocol using an inexpensive, commercially available phosphorus starting material would appreciably expand the available methods for the synthesis of these materials.

We recently discovered that alkali metal alkoxides are efficient catalysts (N_t up to 10^7 h^{-1}) for the carbonyl ester interchange reaction (eq 1).[9] Mechanistic studies showed



(1)

that the alkali metal alkoxide catalysts formed tetrameric and hexameric aggregates in solution, and that the reaction could most easily be described by the coupled transesterification scenario depicted in Scheme 1.

The stepwise nature of the proposed mechanism suggested that if the alkali metal alkoxides could reversibly add to other types of esters, the synthetic utility of the interchange process could be expanded. We report herein that phosphonates are capable partners in a mixed carbonyl P-based ester interchange reaction, and that this leads to a convenient and rapid synthesis of a variety of dialkyl and alkyl methyl methylphosphonates from dimethyl methylphosphonate (DMMP). As with the carbonyl ester interchange reaction, rates for these processes are fast with turnover frequencies (N_t) in excess of 1.5×10^6 h^{-1} observed. Key kinetic and mechanistic experiments are also presented which are consistent with our previously proposed mechanism.[9b]

Results and Discussion

Synthesis of Dialkyl Methylphosphonates. The readily available and purified dimethyl methylphospho-

(1) (a) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon: Oxford, 1991; pp 761−773. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

(2) Krise, J. P.; Stella, V. J. *Adv. Drug Delivery Rev.* **1996**, *19*, 287−310.

(3) Kurihara, N.; Miyamoto, J.; Paulson, G. D.; Zeeh, B.; Skidmore, M. W.; Hollingworth, R. M.; Kuiper, H. A. *Pure Appl. Chem.* **1997**, *69*, 2007−2025.

(4) See for example: Mitchell, A. G.; Nicolls, D.; Walker, I.; Irwin, W. J.; Freeman, S. *J. Chem. Soc., Perkins Trans. 2* **1991**, 1297−1303

(5) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415−430.

(6) Jouko, V.; Heikki, N.; Esko, P. *Synth. Commun.* **1992**, *22*, 271−276.

(7) Froneman, M.; Modro, T. A. *Synthesis* **1991**, 201−204.

(8) For a variety of alternative phosphonate synthetic techniques see, for example: (a) Tuong, par N. T.; Convert, F.; Martin, G.; Chabrier, P. *Bull. Soc. Chem. Fr.* **1965**, 1925−1930. (b) Segall, Y.; Casida, J. E. *Phosphorus Sulfur* **1993**, *18*, 209−212. (c) Müller, E. *Methoden Der Organischen Chemie*; Georg Thieme Verlag: Stuttgart, Germany, 1963; Vol. 12, pp 387−420.

(9) (a) Stanton, M. G.; Gagné, M. R. *J. Am. Chem. Soc.* **1997**, *119*, 5075−5076. (b) Stanton, M. G.; Allen C. B.; Kissling, R. M.; Lincoln, A. L.; Gagné, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 5981−5989.

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Scheme 1

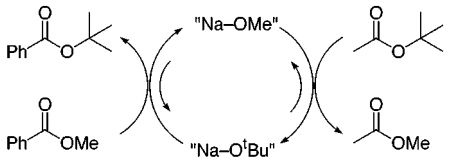
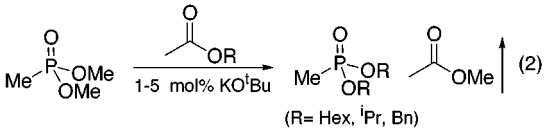
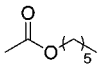
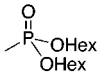
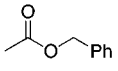
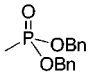
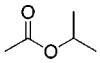
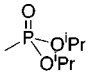


Table 1. Synthesis of Dialkyl Methylphosphonates



entry	ester	method	product	total catalyst[a]	conv(yield)[b]
1[c]		KO^{t}Bu, vacuum		5 mol%	96%(95%)
2		KO^{t}Bu, vacuum		8 mol%	98%(94%)
3[c]		KO^{t}Bu, vacuum		8 mol%	94%(89%)

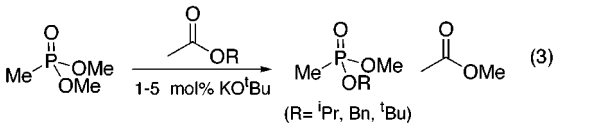
[a]catalyst addition is 1 mol% at a time followed by vacuum to remove MeOAc. [b]conversion by GC, yield represents isolated material of >97% purity. [c]initial ester:DMMP ratio of 1:1 and required substrate recharges along with catalyst.

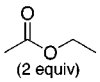
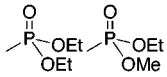
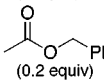
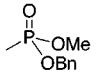
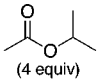
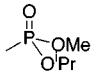
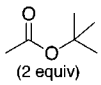
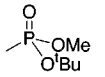
nate (DMMP) is a convenient starting material for the synthesis of dialkyl methylphosphonates via the ester interchange reaction. Using a protocol originally developed for the conversion of methyl to *tert*-butyl esters,[10] we demonstrate herein that simple sterically undemanding *n*-alkyl and isoalkyl acetates are good substrates for the conversion of DMMP to dialkyl methylphosphonates (eq 2, Table 1). Since the interchange process is reversible, mass action and removal of the volatile methyl acetate (MeOAc) ensures a smooth and rapid conversion to the desired product. In cases where the starting ester is also volatile, periodically recharging the reaction vessel helps to push the reaction forward (see Experimental Section).

Large alkoxy groups tend to be problematic due to magnified steric effects in the pentavalent P-ester product. For example, conversion of DMMP to di-*n*-alkyl-substituted P-esters is rapid (seconds), conversion to diisopropyl-substituted P-esters requires more forcing conditions (minutes and vacuum), and synthesis of the di-*tert*-butyl-substituted P-ester has not yet been achieved. Since the KO^{t}Bu catalyst tends to deactivate after several minutes (vide infra), several recharges (up to seven) of 1 mol % catalyst are necessary for high conversion of DMMP and any intermediate alkyl methyl methylphosphonates to the desired product. Optimized protocols for efficient conversion to disubstituted products thus depend primarily on the reactivity (mostly steric) and volatility of the starting ester; nonvolatile esters do not require periodic recharges, and reactive primary esters do not require as many catalyst recharges, Table 1. Optimized reaction conditions enable high conversion (~95%) at high concentrations that simplify workup to salt filtration and purification by passing through a plug or a short column of silica gel. The entries in Table 1 were routinely

(10) Stanton, M. G.; Gagné, M. R. *J. Org. Chem.* **1997**, *62*, 8240−8242.

Table 2. Synthesis of Alkyl Methyl Methylphosphonates



entry	ester[a]	method	product(s)	catalyst	conv(yield)[b]
1	 (2 equiv)	quick quench (5 sec)		5 mol%	-
2	 (0.2 equiv)	quick quench (45 sec)		2 mol%	94%(78%)
3	 (4 equiv)	quick quench (30 sec)		5 mol%	86%(78%)
4	 (2 equiv)	KO^{t}Bu, simultaneous addition		5 mol%	49%(48%)

[a]equivalents of ester are vs. DMMP. [b]conversions are by GC, and yields represent isolated material of >97% purity, and are based on DMMP, except for entry 2.

carried out on a 10 mmol scale in DMMP, and scale-up of entries 2 and 3 to 50 mmol of DMMP proceeded without complication (98 and 94% conversion, 94 and 89% yield, respectively).[11]

Synthesis of Alkyl Methyl Methylphosphonates. Because of the exceptional reactivity of the KO^{t}Bu catalyst for the interchange reaction, the direct synthesis of clean monosubstituted phosphonate products was trickier (eq 3). For example, quenching the reaction of DMMP and EtOAc catalyzed by 5 mol % of KO^{t}Bu after only 5 s led to a statistical mixture of starting material and mono- and disubstituted products (10:50:40, entry 1, Table 2).

Assuming a tetrameric catalyst, two turnovers per productive event, and 6 half-lives to reach equilibrium, the minimum initial turnover frequency (N_t) of 1.5×10^6 is obtained.[12] Rate studies utilizing isopropyl acetate (^{i}PrOAc), however, indicated that the second substitution was sensitive to steric effects and proceeded more slowly than the first (vide infra). Thus, by quickly quenching (30 s) a relatively dilute (~0.3 M) solution of DMMP and 4 equiv of ^{i}PrOAc (entry 3, Table 2), a 7:86:7 mixture of DMMP:isopropyl methyl methylphosphonate (IMMP): diisopropyl methylphosphonate (DIMP) was obtained. Longer reaction times and higher concentrations led to substantial quantities of the undesired diisopropyl methylphosphonate. In the case of *tert*-butoxy substitution (entry 4), the reaction readily proceeds to 50% conversion, and with forcing conditions of additional acetate (5 equiv) and catalyst aliquots (5 equiv) can be pushed to 80−90% conversion. In this case steric effects shut down the second substitution process and cleanly lead to the previously unknown *tert*-butyl methyl methylphosphonate.[13]

Although primary esters did not have sufficiently slowed second substitution rates (k_2) to develop protocols for monosubstitution, esters containing a moderate de-

(11) Dimethyl phenylphosphonate was found to behave similarly, in fact, giving slightly higher rates than DMMP.

(12) This estimate does not take into account the extra turnovers required to convert methyl ethyl methylphosphonate to diethyl methylphosphonate.

(13) Some THF was necessary for reactivity as reactions carried out in neat tBuOAc were sluggish.

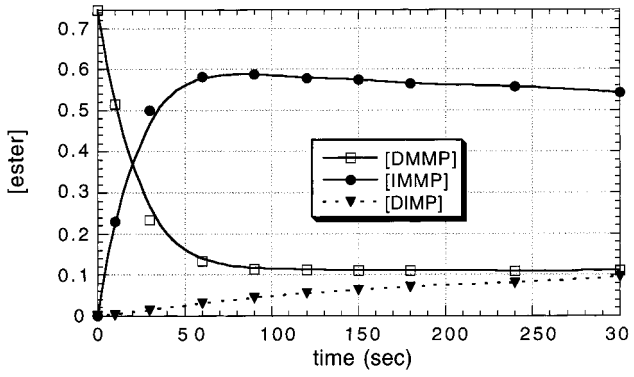
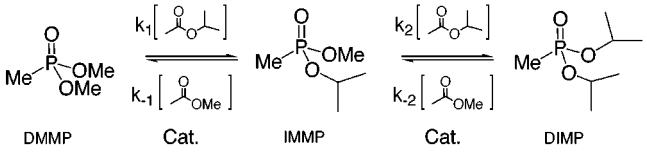


Figure 1. P-Ester concentration vs time for the first 5 min of the reaction in Scheme 2. $[DMMP]_o = 0.745$ M; $[^iPrOAc]_o = 1.49$ M; $[NaO^tBu] = 0.037$ M.

Scheme 2



gree of steric bulk (benzyloxy is sufficient) were amenable to this approach and yielded clean asymmetric products.

Thermodynamics. As mentioned above, the reaction of DMMP with 2 equiv of EtOAc using 5 mol % of KO^t-Bu catalyst reached equilibrium in <5 s, yielding a 10:50:40 mixture of methylphosphonates. Product concentrations were sensitive to changes in the relative concentrations of DMMP and EtOAc in a qualitatively reasonable fashion; however, the fast reaction rates did not allow convenient kinetic studies ($N_t > 1 \times 10^6$ TO h^{-1}). In contrast, measurable rates were obtained using DMMP and ^{i}PrOAc (NaO^{t}Bu, 5 mol %, THF), leading us to choose this reaction for a more careful kinetic and mechanistic analysis.

The scenario in Scheme 2 describes the overall process as two sequential interchanges of methoxide for isopropoxide with concomitant formation of 1 equiv of MeOAc for each interchange. A plot of P-ester concentration vs time (Figure 1) highlights the rapid loss of DMMP and coincident IMMP formation, as well as the slow formation of DIMP. Inspection of the phosphonate concentrations indicated that DMMP and IMMP had established equilibrium in ~100 s, and that after 1 h the IMMP and DIMP concentrations had stabilized. That the latter observation did not represent a thermodynamic mixture of IMMP and DIMP was confirmed by allowing two identical reactions to first mix for 2 h (7:71:22, DMMP:IMMP:DIMP), wherein addition of DMMP (0.2 equiv) to the first reaction did not induce any appreciable changes in the product ratios (27:71:21), addition of fresh catalyst solution (1 mol %) to the second, however, did increase the [DIMP] (6:62:32). This observation clearly implicates a loss of catalytic activity occurs prior to establishing K_2 (Scheme 2), and has previously been observed.[9]

Although the second equilibration (K_2) was not completely established during the course of a kinetic run, it appeared as though the equilibrium between DMMP and IMMP (K_1) was. If this was indeed the case then, once established, the equilibrium should be independent of the slower secondary conversion of IMMP to DIMP. Since our GC analysis accurately measures the relative concentrations of the three P-esters, a time dependent form of the equilibrium expression can be obtained by noting that [MeOAc] is equal to the sum of [IMMP] and twice [DIMP], and that [^{i}PrOAc] is the difference between $[^iPrOAc]_o$ and [MeOAc] (Scheme 2). Substituting these expressions into the equilibrium expression yields K_1 Calc (eq 4), which calculates the equilibrium constant K_1 from readily measured quantities while accounting for the perturbation due to the k_2/k_{-2} process.

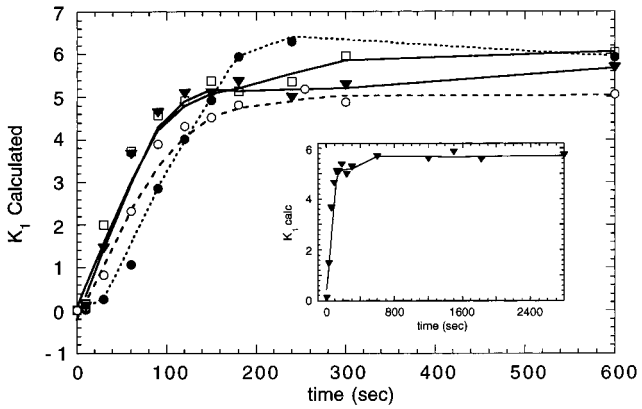


Figure 2. K_1 Calc for Scheme 2 with $[NaO^tBu] = 5$ mol % of the $[DMMP]_o$ for all experiments. $[DMMP]_o = 0.52$ M, $[^iPrOAc] = 3.31$ M (●); $[DMMP]_o = 0.81$ M, $[^iPrOAc]_o = 0.81$ M (□); $[DMMP]_o = 0.75$ M, $[^iPrOAc]_o = 1.49$ M (▼); $[DMMP]_o = 0.64$ M, $[^iPrOAc]_o = 2.53$ M (○). Inset: K_1 Calc of ▼ over 45 min.

$$K_1\ \text{Calc} = \frac{[\text{IMMP}]([\text{IMMP}] + 2[\text{DIMP}])}{[\text{DMMP}]([^i\text{PrAc}]_o - [\text{IMMP}] - 2[\text{DIMP}])} \quad (4)$$

K_1 values calculated using the expression in eq 4 were plotted for a series of reactions that differed in the initial relative concentrations of DMMP and ^{i}PrOAc (Figure 2). Depending on reaction variables, equilibrium concentrations were established within 4−6 min, and for the suite of reactions studied, K_1 converged on a value of 5.6 ± 0.5. The inset in Figure 2 demonstrates that K_1 Calc remains constant over the course of the reaction even though the ester interchange continues to convert IMMP to DIMP after the initial establishment of K_1.

Although the IMMP product is favored based on an entropy of mixing argument,[14] this only predicts a K_1 of 2. The larger observed value suggests that there is also an enthalpic contribution to the free energy difference. The source of this difference is unclear given the steric sensitivity of pentavalent phosphonates (as inferred from synthetic studies, vide supra). The source of the enthalpic contribution is not likely the carbonyl esters, since NaO^t-Bu-catalyzed reactions of methyl benzoate with *tert*-butyl acetate gave a ~1:1:1:1 statistical distribution of starting materials and products (i.e. $K_{eq} = 1$).[9b]

Kinetics. To more fully characterize the reactivity of NaO^{t}Bu in this mixed ester/P-ester interchange reaction, we have also undertaken a kinetic study of the process in Scheme 2. Since the k_2 and k_{-2} processes were slow

(14) Since IMMP is chiral, it therefore has an additional contribution to its entropy equal to R ln 2, the entropy of mixing. See: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds;* John Wiley & Sons: New York, 1994; Chapter 10, p 601.

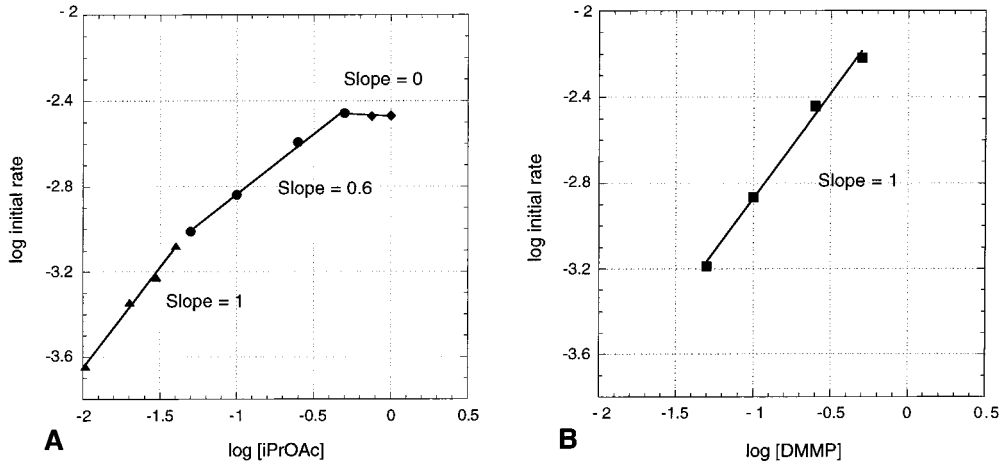
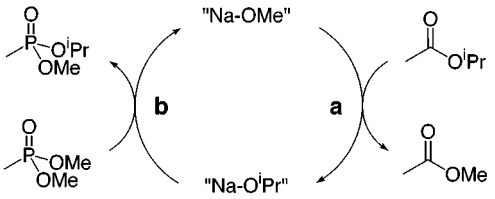


Figure 3. A. Log ν_{init} vs log [ester] for $[DMMP]_o = 0.25$ M and $[^iPrOAc]_o = 0.01-0.04$ M (▲); 0.05−0.25 M (●); 0.50−1.0 M (◆). B. Log ν_{init} for $[^iPrOAc]_o = 0.50$ M, and $[DMMP]_o = 0.05-0.50$ M (■). $[NaO^tBu] = 0.0125$ M in each set of runs.

Scheme 3



compared to k_1 and k_{-1}, we were able to measure initial rates for the conversion of DMMP to IMMP. A series of experiments tracking the loss of DMMP over the first minute allowed us to determine orders in each ester according to the generic rate law in eq 5. In each case

$$\text{rate} = k_{obs}[DMMP]^x[^iPrOAc]^y \quad \text{where} \quad k_{obs} = k[\text{catalyst}]^z \quad (5)$$

the catalyst and second ester concentrations were kept constant to obtain plots of log ν_{init} vs log [ester], Figure 3.

The order of the reaction with respect to ^{i}PrOAc was determined while [DMMP] and [NaO^{t}Bu] were held constant at 0.25 and 0.0125 M, respectively (Figure 3A). A nonlinear order in ^{i}PrOAc was observed which has three distinct regions: a slope of 1 at low concentrations, a slope of 0.6 at mid concentrations, and a slope of zero at high concentrations. This apparent change in order from low to high concentrations of ^{i}PrOAc could be readily rationalized when considered in the context of the two-step transesterification process simplified in Scheme 3. At high [^{i}PrOAc] (0.5−1.0 M), the reaction is zero-order in ^{i}PrOAc, consistent with a fast *a* step and DMMP interchange with NaOiPr (step *b*) being turnover limiting, and "NaO^{i}Pr" being the catalyst resting state. On the other hand, when the concentration of ^{i}PrOAc is low (<0.04 M), step *a* is slowed to the point where step *b* is now faster and transesterification of ^{i}PrOAc with NaOMe is turnover limiting and first-order in ^{i}PrOAc, and "NaOMe" is the catalyst resting state. The intermediate regime (slope of 0.6) most reasonably represents the gradual conversion from step *a* to *b* being turnover-limiting and with a concomitant shift in catalyst resting states from "NaOMe" to "NaO^{i}Pr".

Analysis of the log−log plot for the dependence of the initial rate on [DMMP] (Figure 3B) indicates that at constant [^{i}PrOAc] and [NaO^{t}Bu] (0.50 and 0.0125 M, respectively), the reaction is first-order in DMMP. The ^{i}PrOAc concentration chosen for this study places the reaction order in ^{i}PrOAc cleanly at zero (see Figure 3A), indicating that the overall rate law under these conditions is:

$$\text{rate} = k[NaO^iPr]^1[DMMP]^1[^iPrOAc]^0$$

Presumably, the slope of this log−log plot would also decrease and ultimately reach zero with increasing concentrations of DMMP.

The plot in Figure 3A also indicates that at a [DMMP] of 0.25 M, the [^{i}PrOAc] that completely turns over the order in this ester from 0.6 to 0 is ~0.5 M (from the breakpoint), suggesting that for all [^{i}PrOAc] > 2[DMMP], step *b* in Scheme 3 is turnover-limiting. Conversely, the 1 to 0.6 breakpoint indicates that for all [^{i}PrOAc] < 0.2-[DMMP], the reaction rate is dominated by step *a*. The rate laws for the conversion of DMMP to IMMP can thus be written as:

$$\text{rate} = k[\text{"NaOMe"}]^1[^iPrOAc]^1 \text{ for } [^iPrOAc] < 0.2[DMMP], \text{ and}$$

$$\text{rate} = k[\text{"NaO}^i\text{Pr"}]^1[DMMP]^1 \text{ for } [^iPrOAc] > 2[DMMP]$$

In the intermediate regime, fractional orders in NaOMe, NaO^{i}Pr, ^{i}PrOAc, and DMMP are expected.

Catalyst Structure. When reactions are performed with different alkali metal alkoxides, the rate increases as the cation increases in size from Li to Na to K. This trend parallels an observation in the carbonyl ester interchange reaction that was proposed to be due to enhanced electrostatic interaction in the ground vs excited states.[9b,15] In analogy to the mechanistic experiments carried out on the ester interchange reaction, we propose that tetrameric clusters such as those illustrated below form the dominant aggregates in solution and that

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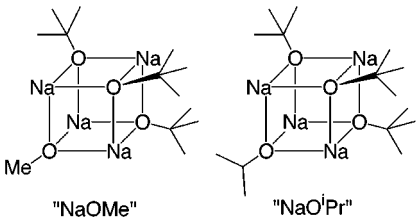
they are the primary reactants in the reversible addition/elimination sequence.[16,17]



Experimental Section

Materials and Methods. All esters were purchased from Aldrich and were purified by distillation from CaH_2 under inert atmosphere prior to use. All alkali metal *tert*-butoxides were purchased from Aldrich, purified by freshly subliming them, and stored in a glovebox. THF was distilled from purple sodium−benzophenone ketyl solution. All other solvents were prepared by first purging reagent grade solvents with argon and dried by passing over a column of activated alumina.[18] Reaction vessels were prepared by flame-drying under a nitrogen purge, and all preparative reactions were conducted under a nitrogen atmosphere. Gas chromatography was performed on HP-5 columns (30 m × 0.32 mm) with ^{1}H, ^{13}C, and ^{31}P NMR spectra obtained at spectrometer frequencies of 300 or 400 MHz. All of the reported phosphonates are known except for *tert*-butyl methyl methylphosphonate; their characterization data are included for completeness.

Dibenzyl Methylphosphonate ($C_6H_5CH_2O)_2P(O)CH_3$. DMMP (50 mmol, 1.08 mL) and benzyl acetate (250 mmol, 36 mL) were syringed into a 250 mL Schlenk flask that had previously been flame-dried under a nitrogen purge. In a separate 250 mL Schlenk flask was prepared a catalyst solution from KO^{t}Bu (4 mmol, 450 mg), hexanes (175 mL), and THF (25 mL). Aliquots of this catalyst solution (20 mL, 1 mol %) were syringed into the phosphonate-bearing flask, stirred for 5 min, and evacuated for 5 min to remove methyl acetate. Addition of catalyst aliquots (20 mL), followed by evacuation of the volatiles, was repeated seven additional times until the desired 98% conversion to product was achieved (confirmed by ^{31}P NMR). The salts were filtered from the ester mixture, and the excess benzyl acetate was separated from the product by distillation at 0.2 mmHg and 35 °C. The product was then purified through a plug of silica gel eluted with 100% ethyl acetate to give 12.9 g of colorless oil in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 10 H), 4.99 (m, 4 H), 1.46 ppm (d, J_{H-P} = 17.7 Hz, 3H); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 136.35 (d, J_{PC} = 7.6 Hz), 128.6, 128.4, 127.9, 67.08 (d, J_{PC} = 6.0 Hz), 11.7 (d, J_{P-C} = 145.0 Hz) ppm; ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$) δ 31.8 ppm; IR (neat) 1242.6 cm^{-1} (P═O).[4]

Diisopropyl Methylphosphonate (^{i}PrO)$_2$P(O)Me. Two separate solutions of isopropyl acetate (400 mmol, 47 mL) in hexanes (115 mL), and KO^{t}Bu (450 mg, 4 mmol, 8 mol %) in THF (40 mL), were prepared in 250 and 50 mL Schlenk flasks, respectively. The reaction was initiated by transferring via syringe solutions of acetate (20 mL, ∼1 equiv) and catalyst (5 mL, 1 mol %) into a 250 mL Schlenk flask containing DMMP (50 mmol, 5.4 mL). The reaction was stirred magnetically for 5 min, and the volatile components were removed in vacuo. The acetate/catalyst addition and evacuation steps were repeated seven additional times to reach a conversion of 94% diisopropyl methylphosphonate and 6% isopropyl methyl methylphosphonate (confirmed by ^{31}P NMR). All volatile material was removed in vacuo, and the phosphonate mixture was filtered from the salts. The product was purified by column chromatography (5% isopropyl alcohol in hexanes), giving 8.0 g of colorless oil in 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68−4.52 (m, 2H), 1.36 (d, J_{P-H} = 17.4 Hz, 3H), 1.23 (d, J_{HH} = 6.3 Hz, 12H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 69.8, 23.9 (d, J_{P-C} = 6.4 Hz), 12.7 (d, J_{P-C} = 145 Hz) ppm; ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$) δ 28.3 ppm; IR (neat) 1244.2 cm^{-1} (P═O).[19]

Benzyl Methyl Methylphosphonate ($C_6H_5CH_2O)(CH_3O)P(O)CH_3$. A reaction solution was prepared by combining DMMP (125 mmol, 13.5 mL), benzyl acetate (25 mmol, 3.62 mL), and 125 mL of THF into a 250 mL Schlenk flask. The reaction was initiated by transferring via syringe a 10 mL THF solution of NaO^{t}Bu (2.5 mmol) to the reaction vessel. After 45 s, the reaction was quenched with saturated brine (2 mL). Under these conditions, 94% of the benzyl acetate is consumed to yield a 94:6 ratio of mono-:dibenzyl methylphosphonate. THF was removed in vacuo, and the mixture of phosphonates was filtered away from the salts. The excess DMMP and unreacted benzyl acetate were removed by vacuum distillation at 0.2 mmHg and 35 °C. Benzyl methyl methylphosphonate was purified by column chromatography (37% acetone in hexanes), giving 3.92 g of pale yellow oil (78% yield relative to benzyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (br s, 5H), 4.98 (m, 2H), 3.57 (d, J_{P-H} = 11.1 Hz, 3H), 1.38 (d, J_{P-H} = 18.0 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 136.4 (d, J_{PC} = 7.6 Hz), 128.6, 128.4, 128.1, 67.1 (d, J_{PC} = 6.0 Hz), 52.1 (d, J_{PC} = 4.0 Hz), 10.8 (d, J_{P-C} = 143.7 Hz) ppm; ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$) δ 32.47 ppm; IR (neat) 1244.3 cm^{-1} (P═O).[8a]

Isopropyl Methyl Methylphosphonate (^{i}PrO)(CH$_3$O)P(O)CH$_3$. A biphasic reaction solution was prepared by combining DMMP (100 mmol, 10.8 mL), isopropyl acetate (400 mmol, 46.8 mL), and 250 mL of hexanes in a 500 mL Schlenk flask under nitrogen. A KO^{t}Bu solution (280 mg, 2.5 mmol, 5 mol % in 50 mL THF) was transferred via syringe into the ester-containing flask, resulting in a cloudy single-phase reaction mixture which was stirred for ∼30 s and then quenched with 1 mL of brine. Under these conditions, IMMP was produced as the major product (DMMP:IMMP:DIMP = 7:86:7). The reaction mixture was decanted away from the salts, solvent and acetates were removed in vacuo, and the product was purified by column chromatography (10% ethanol in hexanes), giving 11.8 g of colorless oil in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (d septet, J_{P-H} = 7.8, J_{H-H} = 6.3 Hz, 1H), 3.47 (d, J_{P-H} = 11.1, 3H), 1.23 (d, J_{P-H} = 17.7, 3H), 1.07 (d, J_{H-H} = 6.3, 6H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 70.1 (d, J_{P-C} = 6.4 Hz), 51.7 (d, J_{P-C} = 6.4 Hz), 23.8, 10.9 (d, J_{P-C} = 145.6) ppm; ^{31}P{^{1}H} (121.5 MHz, $CDCl_3$) δ 30.9 ppm; IR (neat) 1243.5 cm^{-1} (P═O).[6,8b]

***tert*-Butyl Methyl Methylphosphonate ((CH$_3$)$_3$CO)(CH$_3$O)P(O)CH$_3$.** A hexanes solution (100 mL) of DMMP (25 mmol, 2.7 mL) was prepared in a 150 mL three-necked flask under nitrogen. Two pressure-equalizing addition funnels were fitted to the reaction vessel to which were added *tert*-butyl acetate (50 mmol, 6.74 mL) and a 10 mL THF solution of KO^{t}Bu (140 mg, 5 mol %). The acetate and catalyst solutions were each separately dripped into the reaction over ∼5 min. After stirring for an additional 10 min, the reaction solution was a deep golden yellow with small crystals forming on the flask surface. ^{31}P NMR analysis indicated a 49% conversion to product. The solution was decanted, solvent and acetates were removed in vacuo, and the product was purified by column chromatography (30% acetone in hexanes), to give 2.0 g of pale yellow oil in 48% overall yield (>97% purity). High concentrations of *tert*-butyl acetate appear to inhibit catalysis; the slow addition protocol alleviates this. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57 (d, J_{P-H} = 10.4, 3H), 1.38 (s, 9H), 1.31 (d, J_{P-H} = 16.7 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 82.19 (d, J_{P-C} = 8.6 Hz), 51.72 (d, J_{P-C} = 6.1 Hz), 30.35 (d, J_{P-C} = 3.6

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Hz), 12.79 (d, $J_{P-C} = 147.3$ Hz) ppm; $^{31}P\{^{1}H\}$ NMR (121.5 MHz, $CDCl_3$) δ 27.5; IR (neat) 1247.5 (P═O, m), 1054.9 (m), 997.0 (s) cm^{-1}. Anal. Calcd for $C_6H_{15}O_3P$: C, 43.37; H, 9.10 Found: C, 42.99; H, 9.42.

Typical Kinetic Protocol. A typical kinetic run is as follows: To a 25 mL round-bottom flask, flame-dried under argon purge, were added DMMP (5 mmol, 0.54 mL), ^{i}PrOAc (10 mmol, 1.17 mL), 10 μL of decane, and 10 mL of THF. To a separate flame-dried flask (25 mL) was added 24 mg NaO^{t}-Bu (5 mol %, 0.25 mmol) in the glovebox. Under an argon atmosphere the catalyst was dissolved in 8.3 mL of THF and then transferred via syringe into the ester containing solution to initiate the reaction. The progress of the reaction was measured by periodically removing an aliquot (~0.2 mL) from the reaction vessel via syringe and injecting into a vial containing one drop of brine. Each aliquot was diluted with ethyl acetate, and the conversion of DMMP to IMMP and DIMP was determined by GC. The aliquot quenching protocol was carefully optimized to avoid losing DMMP to the water layer. Relative concentrations of the DMMP derivatives were calculated from GC peak ratios corrected for response factor via an internal decane standard.

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Supporting Information Available: Tables of kinetic data; NMR (^{1}H, ^{13}C and ^{31}P) of *tert*-butyl methyl methylphosphonate. This material is available free of charge via the Internet at http://pubs.acs.org.

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